Trends of HIV Infection Among Infants Born to HIV Infected Mothers on PMCT Antiretroviral Treatment in Western Kenya.

*Olipher Makwaga[1], Anne Muigai[2], Freda Andayi[1], Tom Mokaya[1], Joseph Khamala[1], Winnie Ariya[3], Matilu Mwau[1],

1. *Center For Infectious And Parasitic Diseases Control Research, Kenya Medical Research Institute,*
2. *Professor, Department Of Botany, Jomo Kenyatta University Of Agriculture And Technology,*
3. *Maseno University.*

Contacts of the Authors:

OM: oliphermakwaga@gmail.com, P.O. Box 3-50400, Busia, Kenya.
AWM: awmuigai@yahoo.co.uk, P.O. Box 62,000 – 00200 Nairobi, Kenya
FA: andayif@yahoo.com, P.O. Box 3-50400, Busia, Kenya
AM: annemutsami@yahoo.com, P.O. Box 190-50100, Kakamega
TM: mokayatom@yahoo.co.uk, P.O. Box 3-50400, Busia, Kenya
JK: jkhamala@hotmail.com, P.O. Box 3-50400, Busia, Kenya
WA: ariya7.aw@gmail.com, P.O. Box 333 Kisumu, Kenya
MM: matilu.mwau@gmail.com, P.O. Box 3-50400, Busia, Kenya

Corresponding Author– Olipher Makwaga, P.O. Box 3-50400, Busia Kenya. Tel: +254720406703
Email: oliphermakwaga@gmail.com,

Summary

BACKGROUND

More than 365,000 of unborn children are at risk of getting HIV infection in the developing world through "vertical" transmission. Although, ARVs are being used to reduce maternal HIV transmission, limited information exists indicating their impact on the trend of HIV prevalence among infants born to HIV infected mothers.

OBJECTIVE

To determine the trend of HIV infection among infants born to HIV infected mothers in relation to specific ARVs administered to pregnant women and lactating mothers of 18 months and below infants.

METHODOLOGY

Dried blood spot samples in the following quantities per year thus, in 2010, n = 4,210, in 2011, n=4,093, in 2012, n=4,686, in 2013, n=3,080 were collected from infants aged ≤18 months whose mothers were HIV positive. The samples were analyzed using Cobas Polymerase Chain Reaction Assay in early infant diagnosis laboratory at the Center for Infectious and Parasitic Diseases Control Research, Kenya Medical Research Institute (KEMRI).

RESULTS

Out of the total number of samples tested 2010, 409(9.7%) tested HIV positive. In 2011, 350(8.5%), in 2012, 368(7.9%) and in 2013, 221(7.2%) were HIV positive respectively. The trend of HIV in infants whose mothers had been put on various ARVs was as follows: AZT+3TC +EFV,

in 2010, the number was 10.4%. In 2011, it moved to 9.1%, in 2012, to 6.3% and 2013, dropped to 6.0%. AZT+3TC+NVP, in 2010, the number was 7.1%, in 2011, moved to 6.1%, in 2012, falling to 4.7% and 2013 to3.9%. SdNVP, in 2010, the number was 10.3%. In 2011, moved to 7.4%, in 2012, dropping to 6.2% and in 2013, at 6.0%. Those mothers who had not been given any ARVs, their infants had HIV prevalence as follows: in 2010, the number was 11.2%. In 2011, it climbed to 12.6%, moving to 12.7% in 2012, and 12.9% in 2013.

CONCLUSION

There was direct relationship between specific ARV administration and HIV infection among those infants. That was evident by the fact that, HIV appeared to decrease with subsequent years of provision of specific drugs. However, HAART (AZT+3TC+ EFV) seemed to provide greater impact in HIV prevention compared to other HAART (AZT+3TC+NVP) and SdNVP. The worst groups are those not on any ARVs. Single-dose Nevirapine commonly is used for prevention event-hough prior studies have shown exposure to it develop drug resistance, which can compromise the effective not only of itself, but also other non-nucleoside reverse transcriptase inhibitors (NNRTIs)

RECOMMENDATION

There is need for all HIV positive pregnant women to be put on ARVs and monitored for ARVs uptake to reduce the transmission of HIV from mother to child.

Key words: HIV, ARVs, Infants,

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Summary

Introduction

UNAIDS and the World Health Organization (WHO) estimated that in 2009 there were 230,000 to 510,000 new HIV infections worldwide among children aged 0–15 years of age [1].

Over 95% of these infections occurred in resource-limited settings, primarily Sub-Saharan Africa. Up to 90% of the infections resulted from mother-to-child transmission (MTCT) [2].

The World Health Organization estimates the risk of transmission ranges from 15 to 30% in non-breastfeeding populations and from 20 to 45% in breastfeeding populations [3].

Currently more than half of these infants who do not receive treatment die before their second birthday. Scaling up an effective Elimination of MTCT approach globally can reduce rates of transmission to less than 5% annually. It could also avert more than one million new HIV infections among children by 2015, while improving overall maternal and family health [3, 4].

Management of a pregnant woman with HIV infection has evolved significantly over the past 25 years in light of advancements in drug development. Greater understanding to the prevention of perinatal HIV transmission not overlooked. The risk of HIV transmission from mother to infant had declined to historically low levels with the use of Antiretroviral Medications [5, 6]

Pregnant women with HIV infection should receive standard clinical, *immunologic,* and *virologic* evaluation. They should be offered appropriate Antiretroviral therapy for their own health and for prevention of perinatal transmission of HIV, consistent

with the principles of treatment for non-pregnant adults [4, 7-9].

Untreated mothers with a viral load >100,000 copies/ml had a transmission risk of over 50%. The risk when viral loads are < 1000 copies/ml are less than 1%[2, 4, 7].

With the advent of Highly Active Antiretroviral Therapy (HAART), HIV-1 infection is now manageable as a chronic disease in patients who have access to medication and who achieve durable virologic suppression [10].

HAART provides effective treatment options for Treatment - Naive and Treatment - Experienced patients. Also, the use of those Highly Active Antiretroviral Therapy (HAART) regimens has contributed to the decline in morbidity among patients with advanced HIV infection [10, 11]

The use of a combination Antiretroviral therapy (cART) regimen reduces plasma HIV RNA to undetectable levels that do help in lowering of the risk of transmission in an analysis of perinatal transmission in [5,151

HIV - infected women between 2000 and 2006 in the United Kingdom and Ireland's overall perinatal transmission rate was 1.2%. A transmission rate of 0.8% was seen in women on ARV drugs for at least the last 14 days of pregnancy, regardless of the type of ARV regimen or mode of delivery [6].

Similar data from Canada of 1,707 HIV-infected pregnant women followed between 1997 and 2010 showed perinatal transmission was 1% in mothers receiving cART, and 0.4% if more than 4 weeks of cART was received [12].

Two of the cART (AZT/3TC/NVP or EFV) have been evaluated in the context of prevention of mother-to-child transmission of HIV in under resourced settings result in excellent early virological suppression in mothers and those regimens were relatively safe and well tolerated.

That regimen was available and listed in the national guidelines of most low and middle - income countries and recommended for use in pregnant women in need of ART. The most frequently used regimen include 3TC, AZT and NVP or EFV and the most widely used Antiretroviral in combined treatments is 3TC [13].

Furthermore, starting AZT, 3TC, and Nevirapine (NVP) at 34 weeks in a mixed-feeding population has been found to reduce infant HIV-transmission or death at 7 months compared to a short-course regimen (RR 0.39, 95% CI: 0.12-0.85) (Bae, 2008) [14].

Since the efficacy of AZT was first demonstrated in 1994, a gradual decrease of vertical HIV transmission has been observed in Europe and the United States, reducing rates from 25% to below 2% [5, 15, 16].

It is recommended that, AZT+3TC+EFV is one of the preferred regimens for ART-naïve patients initiating ART especially in pregnant women. However, It is not administered during the first trimester of pregnancy [17].

Single-dose Nevirapine is commonly used for prevention of mother-to-child transmission in resource-limited settings, especially for women who do not receive care until the time of delivery. But prior studies have shown that women and infants exposed to a single dose often develop drug resistance, which can compromise the effective not only of Nevirapine itself, but also other non-nucleoside reverse transcriptase inhibitors (NNRTIs) [18].

A single dose of Nevirapine given to both mother and child reduced the rate of HIV transmission by almost 50% in a clinical trial in Uganda[19]. Because of its ease of administering and effectiveness, a single-dose Nevirapine (SD-NVP) was widely used in poorly-resourced countries like sub-Saharan Africa. The drug is administered at the onset of labor, and to the infant directly after birth [17].

When used alone, SD-NVP reduces the rate of mother-to-child transmission by 50%. When used in concert with other drugs, SD-NVP was even more effective- reducing MTCT to as low as >1% (but, adding a high-cost, high-use drug does eliminate the practicality of SD-NVP). That was a simple and inexpensive method of decreasing the number of children infected with HIV in less-developed countries [20, 21]

A subsequent study in Thailand showed that Prophylaxis with single-dose Nevirapine in addition to Zidovudine was more effective than Zidovudine alone [22].

These and other trials have led the World Health Organization to endorse the use of single-dose Nevirapine prophylaxis in many developing world settings as a cost-effective way of reducing mother-to-child transmission. However, in the United States the Ugandan study was deemed flawed [23,24].

Namibia's first PMTCT guidelines of 2004 were based on the use of single dose Nevirapine given to the mother at the onset of labour and a single dose given to the infant between 12 to 72 hours after delivery.

In 2006, WHO released guidelines that recommended the use of combination regimens to improve efficacy of prevention. To this end, it has become necessary to revise Namibia's first edition of the PMTCT guidelines to include the use of more efficacious regimens for PMTCT [25, 26]

Several trials of short-course/single-dose peripartum ARV regimens have reported 18-mo transmission rates between 6.8% and 15.9% [27-29].

In Kenya, the study has found that PMTCT programmes using single-dose Nevirapine administered to both mother and child are effective in reducing the early transmission of HIV in operational settings [30].

Although HIV prevalence among the general population has fallen in Kenya, women continue to be disproportionately affected by the epidemic.

In 2012, 6.9 % of women were living with HIV compared with 4.2 percent of men [31].

Kenya was committed to eliminating the mother-to-child transmission (MTCT) of HIV by 2015. Among the key strategies to Prevent The Mother-To-Child Transmission (PMTCT) of HIV include universal uptake of HIV testing among pregnant women, as well as the provision of Antiretroviral Drugs (ARVs) [32].

Indeed, in recent years, PMTCT efforts in Kenya have expanded rapidly. From 2008 to 2013, 58,000 women annually were offered PMTCT services, out of an estimated 79,000 (76 percent coverage).

Between 2010 and 2013, PMTCT actual coverage fell from 86 percent to 70 percent. Nevertheless, this was due mainly to an increase in demand for PMTCT services [32].

In 2009, the Kenyan government emphasized the importance of male involvement in PMTCT, and in 2010 started a campaign to encourage partner testing, exclusive breastfeeding and the delivery of ART to children [33, 34].

From 2010 to 2013, the percentage of women and their infants given ARVs during breastfeeding to prevent HIV transmission via this route increased from 65 percent to 70.6 percent. By comparison, male involvement in PMTCT remains very low in Kenya only 4.5 percent [32].

In such a country with increasing women and their infants given ARVs to prevent HIV Transmission, it is necessary to subsequently note the success of ARVs in the PMTCT program.

Therefore, the objectives of this study was to determine the trend of HIV infection among infants born to HIV infected mothers in relation to specific ARVs administration among pregnant women and mothers of 18 and below months infants from 2010 to 2013.

Materials and Methodology

Study Site And Population

Samples from referral health facilities (Busia, Bungoma, Kakamega and Vihiga county referral hospitals) in Western part of Keya providing Prevention of Mother - to - Child Transmission (PMTCT) and HIV management services such as HIV testing, CD4 counts, ARVs and anti-TB drugs for both the mothers and their infants were considered for this study.

All these health facilities are located in Western part of Kenya. The study population involved infants aged ≤ 18 months born to HIV-infected mothers. All the samples collected were analyzed in early infant diagnostics laboratory at the Center for Infectious and Parasitic Diseases Control Research, Kenya Medical Research Institute located in Alupe, Busia, Kenya.

Sample Collection

The study utilized samples of the Protocol SSC No. 1066 on Early Infant Diagnosis of HIV. These samples were collected for EID from health

facilities mentioned above and curried in the CIPDCR/KEMRI laboratory. These samples were accompanied by detailed laboratory requisition forms including the details of the infants and their mothers in relation to HIV medications.

Processing Of Samples

For Cobas Assay, analyzing of the samples followed four major processes. 6mm × 2 disks from the DBS were punched and dropped in each tube as folows:

1. Approximately 1100µl of Roche specimen specks was added to each tube.

2. Approximately 1000 µl of negative and low positive controls were added into separate empty tubes and vortexed for 20 seconds.

3. The mixed samples and reagents were thermo-mixed at 560C for 10 minutes at 1000rpm, incubated and loaded onto the COBAS AmpliPrep instrument for sample and control processing.

During this period, all processed samples and controls were not allowed to be exposed to light after completion of sample and control preparation.

Racks containing processed controls, samples and master mix were loaded in the Taqman analyzer within 120 minutes after being processed. After the samples and controls had been analyzed in the Taqman Analyzer, the reports were printed and reported. Flags and error messages were checked.

For HIV negative control, Cobas TaqMan [CTM (-) C] must yield a 'Target Not Detected' result for it to be valid. For low positive control, the assigned titre range for HIV-1 L(+)is specific for each lot of reagents

The HIV-1 low positive controls should fall within the provided ranges. If the positive controls are flagged as invalid, then the entire batch is invalid and the entire process is repeated. For quality control purposes, all the samples that tested HIV-positive were re-tested to confirm their status by the same individual to maintain consistency in sample preparations and analyses.

Data analysis

Data analyses were performed using SPSS® statistical software package version 19.0 (IBM SPSS Inc., Chicago, IL, USA). Simple descriptive statistics was used to calculate frequency. Fleiss' kappa test was used in determining the reliability, accuracy and reproducibility of the repeated tests.

Results

A total of 16069 infants from equivalent number of HIV infected mothers were recruited for the period of four years from four referral hospitals. A total of 3870, 3787, 4241, 4171 were recruited from Vihiga, Busia, Bungoma and Kakamega hospitals respectively *(Table 1).*

Table 1: *Total Number Of Infants Recruited From Each Health Facility*

Referral County hospitals	Vihiga	Busia	Bungoma	Kakamega	Total
2010	901	998	1111	1200	4210
2011	869	984	1150	1090	4093
2012	1200	1106	1300	1080	4686
2013	900	699	680	801	3080
Total	3870	3787	4241	4171	16069

Out of the total 4210; 4093; 4686 and 3080 infants who were recruited in 2010; 2011; 2012 and 2013 respectively (Table 1), 409(9.7%), 350(8.5%); 368(7.9%) and 221(7.2%) were HIV positive respectively (***Figure 1***).

A total of 11,389 (71%) mothers were put on ARVs while 4,680 (29%) were not. In general, mothers who were put on AZT+3TC+EFV (3929) were slightly more compared to those on AZT+3TC+NVP (3627) and SdNVP (3833).

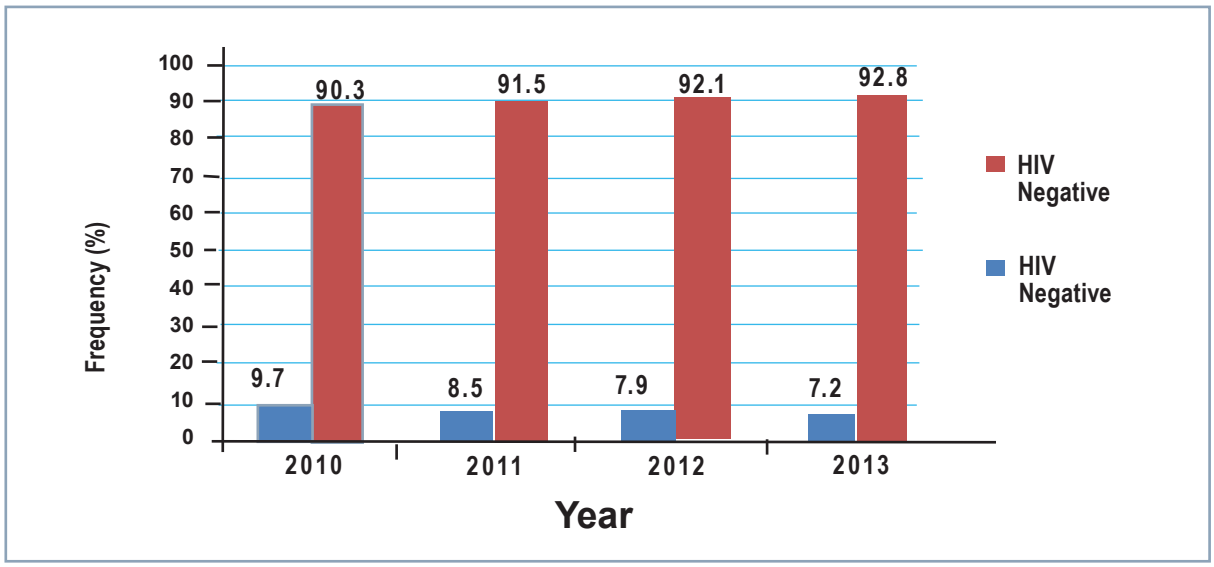

Fig 1: *Trends of HIV Status Of Infants Recruited*

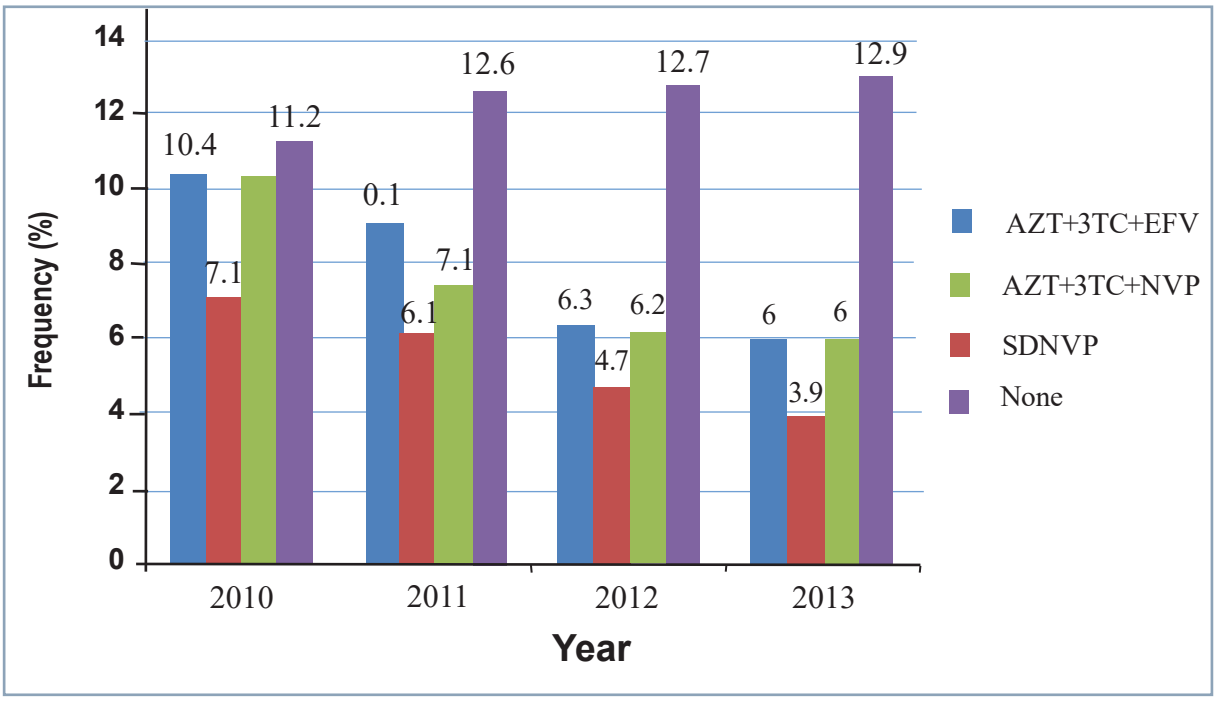

Figure 2: *Trend Of Hiv Infection Among Infants Whose Mothers Were On Various ARVS*

1. Trends of HIV in infants whose mothers were put on AZT+3TC+EFV was:

   2010 - 10.4%,
   2011 - 9.1%,
   2012 - 6.3% and
   2013 - 6.0% respectively.

2. Trends of HIV in infants whose mothers were put on AZT+3TC+NVP was:

   2010 - 7.1%,
   2011 - 6.1%,
   2012 - 4.7% and
   2013 - 3.9% respectively.

3. Trends of HIV in infants whose mothers were put on SdNVP was:

   2010 - 10.3%
   2011 - 7.4%
   2012 - 6.2%
   2013 - 6.0% respectively.

4. However, for the mothers who were not taking any ARVs the trend was:

   2010 - 11.2%
   2011 - 12.6%
   2012 - 12.7%
   2013 - 12.9% respectively.

Table 2: *Differences Of HIV Prevalence Of Infants Whose Mothers Were Taking Specific ARVs*

HIV prevalence difference	HIV prevalence difference	HIV prevalence difference	Average HIV prevalence difference
AZT+3TC+ EFV			
2010 to 2011	***2011 to 2012***	***2012 to 2013***	
1.3	2.8	0.3	1.5
AZT+3TC+ NVP			
1	1.4	0.8	1.1
SdNVP			
2.9	1.2	0.2	1.1
No ARVs uptake			
1.4	0.1	0.2	0.6

Table 2: shows differences of HIV prevalence of infants whose mothers were taking specific ARVs within subsequent years.

1. On average, infants whose mothers were put on AZT+3TC+EFV had 1.5% HIV prevalence reduction
2. while infants whose mothers were put on AZT+3TC+NVP and SdNVP had a reducing transmission prevalence of 1.1% each.
3. Those infants whose mothers were not taking any ARVs had an increasingly transmission of HIV prevalence of 0.6%

Discussion

Pregnant women with HIV infection should receive standard clinical, immunologic, and virologic evaluation. They should be offered appropriate Antiretroviral therapy for their own health and for prevention of perinatal transmission of HIV, consistent with the principles of treatment for non-pregnant adults.

Therefore, the objective of this study was to determine the trend of HIV infection among infants born to HIV infected mothers. This is in relation to specific ARVs administration among pregnant women and mothers of 18 and below months old infants.

The samples were collected from infants attending all the four referral health facilities in Western part of Kenya providing Prevention-of-Mother-to-Child Transmission (PMTCT) and HIV management services. Services such as HIV testing, CD4 counts, ARVs and anti-TB drugs for both mothers and their infants.

Most participants were recruited in 2012 compared to other years. This is perhaps the game changer in 2011 with unprecedented progress in science, political leadership and results for the AIDS response [35, 36].

The recent study shows a decrease in the trends of HIV infections among infants whose mothers were put on various ARVs from 2010 to 2013. Similar pattern to the decreasingly HIV trend of the National [32, 37, 38].

The continuous decrease in HIV infections could be due to various HIV interventions that are being practiced in the health sector [36, 39, 40] and a commitment the leaders have to redouble efforts to achieve a universal access to HIV prevention, treatment, care and support as critical steps towards ending the global HIV epidemic by 2015. Targeting to achieving the Millennium Development Goal 6, in particular to halt and begin to reverse the spread of HIV [35]

The study shows that, a higher percentage (71%) of mothers were put on various ARVs and only 29% were not. This could be due to the degree that, all HIV infected breastfeeding mothers and pregnant women should access PMTCT and be put on ARVS to reduce the scourge [41, 42].

The ART coverage in the current study was more than the global 62% ART coverage probably due to the PMTCT interventions [36, 39, 40]. unlike lower than the coverage of 90% for four prioritized countries, namely Botswana, Ghana, Namibia and Zambia [43].

In general the number of mothers who were taking the three types of ARVs were comparable and almost similar due to the fact that all the three regimens are available and listed in the national guidelines of most low and middle income countries. They are also recommended for use in pregnant women who need ART [44].

In the current study, the trend of HIV is seen to decrease with subsequent years among infants whose mothers were put on ARVS and increase among infants whose HIV positive mothers were not taking ARVs. This supports the idea that ARVs uptake reduces HIV transmission from mothers to their children [45-47]

The reduction of the rate of transmission within subsequent years was seen to be higher among infants whose mothers were put on combined ART therapy (AZT+3TC+ EFV) than combined ART therapy (AZT+3TC+ NVP) and Single dose Nevirapine. Possible explanations for these findings include the greater antiviral activity of EFV versus NVP [48].

Although AZT+3TC+NVP is relatively safe, well tolerated and gives excellent virological suppression in mothers [44]. Some studies have found EFV to result into slightly less side effects and more likely to prevent death than NVP.

To add on that, AZT+3TC+ EFV is associated with less risk of resistance when comparing with AZT+3TC+ NVP and SdNVP [49]

Limitation of the study

Part of our limitation was that we did not investigate why some mothers were not put on ARVs. Some confounding factors like breastfeeding, caesarean type of delivery which might have affected the trend of HIV transmission from mothers to infants were not investigated.

Conclusions

There is a direct relationship between specific ARV administration and HIV infection among these

infants. This is evident by the fact that HIV appeared to decrease with sub-sequent years of provision of specific drugs. HAART (AZT+3TC+EFV) seemed to provide greater impact in HIV prevention compared to other two ARVs. There is need for all pregnant women to be put on ARVs to reduce the transmission of HIV from mothers to their infants.

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